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COMPLETE SPECIFICATION

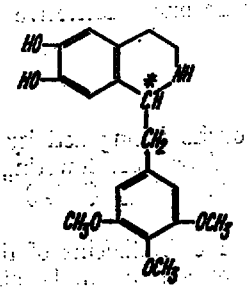
Optical Resolution of 1-(3,4,5-Trimethoxybenzyl)-6,7-Dihydroxy-1,2,3,4-Tetrahydroisoquinoline

We, TANABE SEIYAKU COMPANY LIMITED, a Company registered under the Laws of Japan, of 21 Doshe-machi 3-chome, Higashi-ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the optical resolution of racemic 1 - (3,4,5 - trimethoxy - benzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetra - hydroisoquinoline. More particularly, the invention relates to a process for preparing a diastereomeric salt of an optically active form of 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline with an optically active organic acid and releasing the optically active components from the salt.

We have found that certain acid addition salts of 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline (hereinafter designated as the tetrahydroiso - quinoline derivative) have a very active bronchodilator effect compared with known compounds. The hydrochloride of the compound is approximately ten times as active as isoproterenol *in vitro* and approximately five times *invivo*. The compounds have also a long term cardiotonic activity, while the acute toxicity is very low.

The compound can be synthesized by reacting 2 - (3,4 - dihydroxy - phenyl) - ethylamine with 3,4,5 - trimethoxyphenyl - acetaldehyde under acid conditions. The tetrahydroisoquinoline derivative thus prepared is a racemate of two optically active enantiomers, since the derivative has an asymmetric carbon atom at the 1st position of its isoquinoline skeleton as shown by the formula;



An object of the present invention is to provide a method for the resolution of the racemate of said tetrahydroisoquinoline derivative into optically active d - (+) and l - (−) forms. Another object is to provide a method for separating therapeutically more active l - (− form of the tetrahydroisoquinoline derivative from less active antipode thereof.

According to the present invention, the resolution of the d l - tetrahydroisoquinoline derivative is carried out by treating the racemate with an optically active organic acid in solutions to cause the formation of the corresponding diastereomeric salts thereof, and separating the diastereomeric salts by fractional crystallization. If desired at least one of the separated diastereomeric salts may be treated with an inorganic acid to form the corresponding inorganic acid addition salt.

In a preferred embodiment of the present invention, a racemate of the tetrahydroiso - quinoline derivative is treated with d - tartaric acid in a solvent, thereby two diastereomeric salts, namely l - tetrahydro - isoquinoline derivative d - tartarate and d - tetrahydroisoquinoline d - tartarate, are formed in the solution. As the resolution solvent, an alkanol, for example methanol, ethanol, an

[Price 4s. 6d.]

alkyl acetate for example ethyl acetate; an alkyl ketone for example acetone; mixtures of the organic solvents just mentioned; water or mixture of water and one or more of the above organic solvents just mentioned, for example aqueous methanol, aqueous ethanol, aqueous acetone are suitable.

The diastereomeric salts thus formed are sufficiently different from each other in their solubilities and can be separated in turn from the solution by fractional crystallization. The l - isomer d - tartarate usually crystallizes out first from the solution and d - isomer d - tartarate is recovered by condensing the mother liquor separated from the former diastereomeric salt. Then, the desired d- and l - isomers of the tetrahydroisoquinoline derivative are respectively released by treating the diastereomeric salts with an inorganic acid, preferably with hydrochloric acid or sulfuric acid. The liberation of the isomeric tetrahydroisoquinoline derivative can be accomplished preferably by the introduction of the isolated diastereomeric salt into alcoholic hydrohalic acid (e.g. hydrochloric acid), or by the introduction of gaseous hydrohalic acid into an alcoholic suspension containing said diastereomeric salt.

When carrying out the resolution process, it is usually preferable to use molar equivalents of racemate and optically active acid or a slight molar excess of optically active acid to the racemate. However, the proportions are not critical.

The l - (—) tetrahydroisoquinoline derivative thus obtained in the form of hydro - chloride showed about a three times stronger bronchodilating activity and about a two times stronger blood pressure-lowering activity than its racemate, the acute toxicity being slightly increased. The pharmacological comparison of the optically active enantiomers and the racemate is shown in Table I.

TABLE I

	d l-form	l-form	d-form
Bronchodilating activity	1	3.3	0.087
Blood pressure lowering activity	1	2	0.01
Acute toxicity (LD_{50})	143 mg/kg	112 mg/kg	162 mg/kg.

In the further embodiments of the present invention, the resolution can be also carried out by using other conventional optically active organic acids such as l - tartaric acid, dibenzoyl - D - tartaric acid, D - (—) quinic acid, D - 10 - camphorsulfonic acid as the resolving agent instead of d - tartaric acid.

The starting free base of a d l - tetrahydro - isoquinoline derivative may be conveniently prepared by treating the acid addition salt thereof with an alkali in an aqueous solvent and extracting the reaction mixture with a suitable solvent such as chloroform, ethyl acetate for the purpose of resolution. However, the extraction of said free base is not necessarily required, since the liberated free base in the reaction mixture can be used *in situ* for the succeeding resolution procedures.

EXAMPLE 1

5 g. of a d l - 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroiso - quinoline hydrochloride was dissolved in 500 ml. of water. The solution was made alkaline by adding a proper quantity of the saturated solution of sodium bicarbonate under ice cooling and the resulting free base was extracted with chloroform.

The chloroform solution of d l - 1 - (3,4, - 5, - trimethoxybenzyl) - 6, 7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline was dried with anhydrous sodium sulfate, and a solution containing 2.25 g. of d - tartaric acid in 100 ml. of ethanol was added to the chloroform solution. Then, the mixture was evaporated under reduced pressure to remove solvents and 100 ml. of methanol was added to the residue to cause selective crystallization. The crystals were collected by filtration, washed with a small quantity of methanol, and dried. Thus, 3.21 g. of crude crystals (A) decomposing at 220—223°C. were obtained. On the other hand, 3.37 g. of viscous substance (B) was obtained by evaporating the mixture of the mother liquor and the washings to dryness.

3.21 g. of the crude crystals (A) were recrystallized from aqueous methanol whereby 2.66 g. of l1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroiso - quinoline d - tartarate was recovered as slightly yellowish scales.

Mp. 227—228°C. (decomp.)

$[\alpha]_D^{21}=0$ (C=1, H_2O)

Analysis calculated for $C_{28}H_{29}O_{11}N$: C. 55.75; H, 5.90; N, 2.83
Found: C, 55.54; H, 5.70; N, 3.03

2.66 g. of the crystals were suspended in 20 ml. of methanol and dry hydrogen chloride gas was introduced to the suspension under ice cooling until the crystals disappeared. The solution was evaporated under reduced pressure to dryness and the residue was recrystallized from a mixture of methanol and ether. The crystals were dried over phosphorous pentoxide under reduced pressure (2mmHg) at 95—100°C for three days

whereby 1.24 g. of l - 1 - (3,4,5 - trimethoxy - benzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetra - hydroisoquinoline hydrochloride was obtained as colorless prisms.

Mp. 151—153°C. (decomp.)

$[\alpha]_D^{23} = -30°$ (C=1, methanol)

Analysis calculated for $C_{19}H_{24}O_5NCl$.
: C, 59.76; H, 6.34; N, 3.67; Cl, 9.23
Found: C, 59.50; H, 6.47; N, 3.62; Cl, 9.01

3.37 g. of the viscous substance (B) obtained in the above procedure was dissolved in 10 ml. of methanol and 10 ml. of ether was added to the solution. The mixture was allowed to stand overnight at room temperature. The precipitated small quantity of a mixture of crystalline and viscous substance was filtered off. The filtrate was evaporated under reduced pressure to dryness, whereby 3.25 g. of d - 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroiso - quinoline d - tartarate was obtained as slightly yellowish viscous substance.

$[\alpha]_D^{21} = +16.4°$ (C=1, H_2O)

The substance was dissolved in 20 ml. of methanol, and 3 ml. of methanolic hydrogen chloride was added to the solution under ice cooling. The mixture was evaporated under reduced pressure to dryness and the residue was recrystallized from a mixture of methanol and ether. The crystals was dried over phosphorous under reduced pressure (2 mmHg) at 95—100°C. for three days whereby 1.37 g. of d - 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline hydrochloride was obtained as colorless prisms.

Mp. 151—153°C. (decomp.)

$[\alpha]_D^{22} = +29.20$ (C=1, methanol)

Analysis calculated for $C_{19}H_{24}O_5NCl$.
: C, 59.76; H, 6.34; N, 3.67; Cl, 9.23.
Found: C, 59.46; H, 6.36; N, 3.73; Cl, 9.49.

EXAMPLE 2

8.39 g. of d - tartaric acid and 18.70 g. of d l - 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline hydrochloride were successively dissolved in 190 ml. of water at 70—75°C. 4.12 g. of sodium bicarbonate was dissolved into the solution and the mixture was stirred for 30 minutes. The mixture was cooled and allowed to stand overnight. The resultant tartarate was collected by filtration, washed with water and dried. Thus, 11.62 g. of crude crystals of l - 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline d - tartarate were obtained. The product was recrystallized from hot water whereby 9.65 g. of the crystals melting at 229—232°C. were obtained.

9.11 g. of recrystallized crystals was suspended on 27 ml. of methanol and dry hydrogen chloride gas was introduced into the suspension while maintaining the temperature at lower than 10°C. until the crystal disappeared. The solution was evaporated under reduced pressure into dryness. 8 ml. of methanol was added to the residue and the mixture was allowed to stand overnight. The resultant crystals were collected by filtration and dried whereby 6.34 g. of l - 1 - (3,4,5 - trimethoxy - benzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetra - hydroisoquinoline hydrochloride was obtained. An additional 0.81 g. of the compound was recovered from the mother liquor by adding ether. Both crystals were recrystallized from hot water whereby 7.07 g. of purified l - 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline hydrochloride monohydrate was obtained.

Mp. 149.5—150.5°C. (decomp.)

$[\alpha]_D^{20} = -29.42°$ (C=1, methanol)
$= -18.69°$ (C=1, H_2O)

Water content: 4.82%

The products of the invention may be provided in the form of pharmacological compositions in which the addition salt is associated with a therapeutically acceptable carrier. Such carriers may be foodstuffs, liquids in which the salts are dissolved to render them suitable for administration orally or by objection, pulverulent diluents yielding compositions, which may be formed into pills or tablets for oral administration or soluble capsules.

WHAT WE CLAIM IS:—

1. A process for the production of an optically active acid addition salt of 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4, - tetrahydroisoquinoline which com-

whereby 1.24 g. of l - 1 - (3,4,5 - trimethoxy - benzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetra - hydroisoquinoline hydrochloride was obtained as colorless prisms.

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$= -18.69°$ (C=1, H_2O)

Water content: 4.82%

The products of the invention may be provided in the form of pharmacological compositions in which the addition salt is associated with a therapeutically acceptable carrier. Such carriers may be foodstuffs, liquids in which the salts are dissolved to render them suitable for administration orally or by objection, pulverulent diluents yielding compositions, which may be formed into pills or tablets for oral administration or soluble capsules.

WHAT WE CLAIM IS:—

1. A process for the production of an optically active acid addition salt of 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4, - tetrahydroisoquinoline which com-

* C L M S *

prises treating a racemate of the compound with an optically active organic acid in a solution, and separating the resultant diastereomeric salts by fractional crystallization.

2. A process according to Claim 1 wherein at least one of the diastereomeric salts is further treated with an inorganic acid to form the corresponding inorganic acid addition salt.

3. A process according to either of Claims 1 or 2 wherein said organic acid is d - tartaric acid.

4. l(—) 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroiso - quinoline d - tartarate.

5. l(—) 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroiso - quinoline hydrohalide.

6. A process for the production of an optically active acid addition salt of 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline, substantially as hereinbefore described and illustrated by reference to the foregoing Examples.

7. An optically active acid addition salt of 1 - (3,4,5 - trimethoxybenzyl) - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline when prepared by a process in accordance with any one of Claims 1 to 3.

8. An optically active acid addition salt according to any one of Claims 4, 5 or 7 in association with a therapeutically acceptable carrier therefor.

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